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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KUMAR *et al.*	Atty. Dkt. No.:	RLL-266US
Serial No.:	10,517,101	Group Art Unit:	Unknown
Filing Date:	December 7, 2004	Examiner:	Unknown

Title: A METHOD OF MAKING CONTROLLED RELEASE TABLETS OF VENLAFAXINE

Certificate of Mailing

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Kim Campbell

Kim Campbell

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 1157/Del/2002 filed 15 November 2002 (15.11.2002) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: William D. Hare

William D. Hare, Esq.
Patent Counsel – Intellectual Property

Dated: February 18, 2005

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INTELLECTUAL PROPERTY **INDIA**

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NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1157/Del/2002*** *dated* ***15th November 2002.***

Witness my hand this 3rd day of February 2005.

(M.R. GUPTA)
Assistant Controller of Patents & Designs

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1157 DEL 02

FORM 1

15 NOV 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A NOVEL METHOD OF PREPARING MODIFIED RELEASE MULTIPLE UNIT SYSTEM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PRATIK KUMAR

b. RAVIKUMAR NITHIYANANDAM

c. ASHOK RAMPAL

DUPLICATE

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, PRATIK KUMAR, RAVIKUMAR NITHIYANANDAM, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Pratik Kumar

(PRATIK KUMAR)

b. N. Ravikumar

(RAVIKUMAR NITHIYANANDAM)

c. A. Rampal

(ASHOK RAMPAL)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.**5,000/-** (Rupees Five Thousand only..) in cheque bearing No. **685644** dated **05.11.2002** on ANZ Grindlays Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this **14TH** day of **November,** 2002.

For Ranbaxy Laboratories Limited

~~(SUSHIL KUMAR PATAWARI)~~
~~Company Secretary~~

Vinay Kumar Kaul

1157 DEL 02

FORM 2

15 NOV 2002

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A NOVEL METHOD OF PREPARING MODIFIED RELEASE MULTIPLE UNIT SYSTEM

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

This invention relates to a novel method of preparing modified release multiple unit system, which can be easily compressed into tablet or filled into capsule/sachet without affecting the desired release characteristics.

The need of modified release formulations for better clinical outcome is well documented in the prior art. This is particularly important for drugs with short half-lives, having region specific absorption or producing gastric irritation or other side effects at high plasma concentrations.

One of the most common methods of achieving modified drug release involves the use of monolithic systems endowed with modified release characteristics. These monolithic systems vary from osmotic drug delivery systems to bioerodible or non erodible matrix based systems.

Though a major portion of modified release formulations today are monolithic systems, they suffer from few serious drawbacks. Intentional or accidental breakdown of the delivery system is one of the limitations that may cause dose dumping. Dose dumping leads to toxic effects, which are sometimes even fatal. Further, the gastric emptying of the comparatively large monolithic systems is variable, depending on the presence or absence as well as the type of food taken by the patient.

These disadvantages have prompted a shift in modified release technology from the use of monolithic systems to multiple unit systems, wherein each individual unit is formulated with modified release characteristics. The final dosage form constitutes of a collection of the multiple units, compressed into tablet, or filled into capsule/sachet. When administered, the individual units are dispersed freely into the gastrointestinal contents avoiding high local concentration of drug, which may lead to irritation of gastrointestinal mucosa. Also, the performance of the dosage form is independent of inter and intra patient variability in gastric emptying time, due to the small size of individual units. This technology has an added advantage of division of doses without formulation and process changes, delivery of incompatible agents together in a single dosage form and delivery of particles with different release characteristics to achieve desired release profile.

Each unit of the multiple unit system is either

a. an inert core/pellet coated with one or more layers of drug and other release controlling polymeric substances; or

b. Drug-containing core/pellet optionally coated with one or more layers of release controlling polymeric substances.

A common problem with modified release multiple unit systems is the rupturing or cracking of release controlling layers/membrane or fragmentation of the core due to mechanical stress generated during compression of cores to tablet or filling into capsule/sachet.

Various approaches are described in the prior art for formulating multiple unit systems with desired mechanical strength. For example US Pat. No. 4,713,248 discloses water-based film comprising a homogenous combination of water dispersible film forming agent and a polymeric substance over a controlled release multiple unit formulation containing an active substance.

On the other hand, US Pat. No. 5,783,215 describes the use of inert and non-soluble cores of glass or sand particles or soluble cores such as sugar spheres capable of withstanding mechanical stress, in combination with a plasticizing layer of a hydrophilic polymer containing the drug, optionally with additional layers of the polymer not containing the drug, layered between the core and the release controlling membrane.

However, there still exists a need for a universal multiple unit systems of desired mechanical strength.

Therefore, the present invention relates to a method for preparation of modified release multiple unit system, which can be easily compressed into tablet or filled into capsule/sachet without affecting the desired release characteristics of drug. In the present invention the problems associated with the mechanical stress due to compression or filling as mentioned above has been overcome by giving an outermost non-functional coating of a waxy material to each unit of multiple unit system. We have found that nonfunctional coating of a waxy material to each unit

gives favorable mechanical properties withstanding cracking especially of the release controlling membrane when exposed to mechanical stress for example during compression into tablet or filling into capsule/sachet.

The waxy coating imparts elasticity and compressibility to the units and makes possible the compression of the multiple units into tablet or filling into capsule/sachet without altering the dissolution profile and hence the bioavailability and clinical effects.

Further, this novel approach can be used over any type of pre-functional layers and irrespective of drug characteristics.

Hence the present invention provides a method for the preparation of modified release multiple unit system comprising a final non-functional coating of a waxy material; which can be easily compressed into tablet, or filled into capsule/sachet without affecting the desired release characteristics of drug.

The waxy material of the present invention may be selected from the range of polyethylene glycols (PEGs) of various molecular weights such as PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like.

The amount of the waxy material may vary from about 1 % to about 100 % by weight of the weight of individual unit. The waxy layer is applied as solution/suspension using any conventional coating technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating to the each unit of multiple unit system. Alternatively, the waxy layer may also be applied using hot melt technique.

The solvents used for making a solution/suspension of the waxy material for the purpose of present invention may be selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

The multiple units of the present invention may contain inert cores; or a drug containing cores, wherein the drug is incorporated within the cores.

The inert core of the present invention is either a commercially available product or prepared in the laboratory. The inert core may be of any geometric shape, though spherical beads are preferred for the ease of uniform coating. The bead diameter may vary from about 100 to 700 µm.

The commercially available inert cores may be selected from sugar spheres, non pariel seeds, celpheres and the like.

Methods of manufacturing the inert core or drug containing core include:

a. Extrusion-Spheronization: The inert core material with or without drug and other pharmaceutical excipients is granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a screen. The extrudates are spheronized in a marumerizer. The resulting spheroids/pellets are dried and sieved for further applications.

b. Granulation: The inert core material with or without drug and other pharmaceutical excipients is dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

The inert core material of the present invention may be selected from pharmaceutically inert insoluble, soluble or swellable material. The insoluble inert cores are composed of sand (silicon dioxide), glass, microcrystalline cellulose (celpheres) or plastic (polystyrene) material. On the other hand soluble inert cores are composed of sugar selected from glucose, mannitol, lactose, xylitol, dextrose, sucrose and the like. The swellable inert cores are composed of hydroxypropyl methylcellulose.

Alternatively, drug-containing cores can also be prepared by replacing inert core material with drug(s) in the above two methods of preparing inert cores.

The modified release multiple units may be prepared from inert cores by:

- coating inert core with drug and rate controlling polymer; or
- coating inert core with drug layer and rate controlling polymer layers separately.

Both above options may contain a seal coat between inert core and drug layer or between drug layer and rate controlling polymer layer.

The modified release multiple units may be prepared from drug containing cores by:

- coating drug containing core with rate controlling polymer; or
- coating drug containing core with drug and rate controlling polymer.

Both above options may contain a seal coat between drug containing core and rate controlling polymer layer or over rate controlling polymer layer.

The final modified release units of the present invention are prepared by applying a final layer of a waxy material over each unit prepared by the above processes.

The drug layer of the present invention composes of drug(s) and optionally includes other pharmaceutically acceptable excipients. The drug layer may be applied as aqueous/non-aqueous solution or dispersion of drug in water/organic solvent or mixtures thereof. Drug(s) of the present invention may be selected from antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

Illustrative examples of drugs of above classes include enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

The rate controlling polymer layer of the present invention comprises of one or more polymers with or without other pharmaceutically acceptable excipients. This layer may be applied as aqueous/non aqueous solution or dispersion of polymers in water/organic solvent. The polymers of the present invention may be selected from cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose; waxes; hydroxypropylmethyl phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; methacrylic acid polymers such as Eudragit ® RL and RS; and mixtures thereof. The single drug and rate controlling layer may contain above described drug and polymers in the same layer.

The seal coat of the present invention may be composed of polymers selected from hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers and the like.

The modified release units prepared by any of the above methods can be mixed with other pharmaceutically acceptable excipients (if required) and compressed into tablet or filled into capsule/sachet using techniques known in the art for these purposes. The final tablet or capsule may optionally be coated, if desired.

The other pharmaceutically acceptable excipients as used herein include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers and coloring agents.

Surfactants of the present invention may be selected from non-ionic surfactants such as mono fatty acid esters of polyoxyethylene sorbitan, for example, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20); anionic surfactants, for example, sodium lauryl sulfate; polyoxyethylene castor oil derivatives, for example polyoxyethyleneglycerol triiricinoleate or polyoxyl 35 castor oil (Cremophor EL); and Vitamin E TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate) and the like.

Binders of the present invention may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Diluents of the present invention may be selected from calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Lubricants and glidants of the present invention may be selected from colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like.

Plasticizers of the present invention may be selected from polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate and the like.

Stabilizers of the present invention may be selected from antioxidants, buffers, acids and the like.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention any way.

EXAMPLE 1

(A) Modified release multiple units:

(i) Inert core	
Non pareil seeds	65 mg
(ii) Drug layer	
Venlafaxine hydrochloride	171 mg (equivalent to 150 mg of venlafaxine)
Magnesium stearate	15 mg
Colloidal silica	25 mg
Hydroxypropyl methylcellulose	15 mg
Water q.s.	
iii) Rate controlling layer	
Ethyl cellulose	93.12 mg
Hydroxypropyl methylcellulose	23.28 mg
Triacetin 1% (of total polymers)	
iv) Wax layer	
Polyethylene glycol 6000	30.55 mg

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica, Magnesium stearate and Hydroxypropyl methylcellulose were added to it under stirring.
2. Non pareil seeds were loaded in Glatt Wurster column and coated with drug dispersion of step 1.
3. Drug coated pellets of step 2 were coated with a mixture of Ethyl cellulose and Hydroxypropyl methylcellulose dissolved in a mixture of isopropyl alcohol and methylene chloride.
4. Coated pellets of step 3 were then coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Modified release multiple units of (A)	438 mg
Silicified microcrystalline cellulose	217 mg
PEG 4000	80 mg
Crospovidone	90 mg
Magnesium stearate	5 mg

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablet.

The compressed tablets prepared according to Example 1 had an acceptable hardness of about 7-13 Kp and disintegration time of around 5 minutes. Table 1 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to example 1.

Table 1. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine from	
	Modified release multiple units	Tablets
1	14	17
2	32	33
4	59	57
6	72	69
8	82	79
12	94	91
16	100	97
20	100	100

As shown in Table 1 above, the compression of modified release multiple units into tablets did not alter the sustained release pattern of venlafaxine.

EXAMPLE 2

(A) Modified release multiple units:

(i) Inert core	
Non pareil seeds	65 mg
(ii) Drug layer	
Venlafaxine hydrochloride	171 mg (equivalent to 150 mg of venlafaxine)
Magnesium stearate	13.5mg
Colloidal silica	19.7 mg
Hydroxypropyl methylcellulose	13.5 mg
Water q.s	
iii) Rate controlling layer	
Ethyl cellulose	93 mg
Hydroxypropyl methylcellulose	24 mg
Triacetin 1% (of total polymers)	
iv) Wax layer	
Polyethylene glycol 6000	30 mg

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica, Magnesium stearate and Hydroxypropyl methylcellulose were added to it under stirring.
2. Non pareil seeds were loaded in Glatt and coated with drug dispersion of step 1.
3. Drug coated pellets of step 2 were coated with a mixture of Ethyl cellulose and Hydroxypropyl methylcellulose dissolved in a mixture of isopropyl alcohol and methylene chloride.
4. Coated pellets of step 3 were then coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Modified release multiple units of (A)	473 mg
Silicified microcrystalline cellulose	288 mg
PEG 6000	71 mg
Crospovidone	102 mg
Magnesium stearate	6 mg

Procedure: The modified release multiple units of A were mixed with other excipients and compressed to form tablet.

The compressed tablets prepared according to Example 2 had an acceptable hardness of about 7-13 Kp and disintegration time of around 5 minutes. Table 2 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to example 2.

Table 2. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine from	
	Modified release multiple units	Tablets
1	7	7
2	18	20
4	43	44
8	65	71
12	75	80

As shown in table 2 above, the compression of modified release multiple units into tablets did not alter the sustained release pattern of venlafaxine.

EXAMPLE 3

(A) Modified release multiple units:

(i) Inert core	
Celpheres	148 mg
(ii) Drug layer	
Glipizide	10 mg
Polyethylene glycol	4.7mg
Hydroxypropyl methylcellulose	1.7 mg
Polyvinyl pyrrolidone	3.0 mg
Tween 80	0.5 mg
Lactose	3.0 mg
iii) Rate controlling layer	
Ethyl cellulose	8 mg
Hydroxypropyl methylcellulose	4 mg
Triacetin	1.3 mg
Talc	0.4 mg
iv) Wax layer	
Polyethylene glycol 6000	13.9 mg

Procedure:

1. Polyethylene glycol, Hydroxypropyl methylcellulose, Polyvinyl pyrrolidone, Tween and lactose were dissolved in water and glipizide was then dispersed in the above solution.
2. Celpheres were loaded in Glatt and coated with drug dispersion of step 1.
3. A solution of Ethyl cellulose, Hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which Talc was dispersed.
4. Drug loaded pellets of step 2 were then coated with dispersion of step 3 using a Glatt.
5. Coated pellets of step 4 were then coated with a solution of PEG 6000 in mixture of isopropyl alcohol and methylene chloride.

(B) Compressed tablet:

Modified release multiple units of A	197.4 mg
Silicified microcrystalline cellulose	122.4 mg
Crospovidone	43.4 mg
Polyethylene glycol 6000	29.6 mg
Magnesium Stearate	2.0 mg

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablet

The compressed tablets prepared according to Example 3 had an acceptable hardness of about 8-10 Kp and disintegration time of around 3 minutes. Table's 3a and 3b illustrate the comparative release patterns *in vitro* for modified release multiple units and tablets respectively, prepared according to example 3.

Table 3a. *In vitro* release pattern of modified release multiple units using USP apparatus – II, at 50 rpm and pH 7..5

Time (Hours)	Cumulative percentage release of glipizide from modified release multiple units
1	6
2	13
4	23
8	45
12	62
16	78
20	94
24	102

Table 3b. *In vitro* release pattern of tablets using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from tablets
0.3	3
2.3	18
6.3	44
10.3	65
14.3	83
18.3	100
22.3	107

As shown in table's 3a and 3b above, the compression of modified release multiple units into tablets did not alter the sustained release pattern of glipizide.

Hence, above examples clearly illustrate that the process of present invention provides modified release multiple unit systems, which can withstand mechanical stress without affecting the desired release characteristics.

WE CLAIM:

1. A method for the preparation of modified release multiple unit system comprising a final non-functional coating of a solid waxy material; which can be easily compressed into tablet, or filled into capsule/sachet without affecting the desired release characteristics of drug.

2. The method according to claim 1 wherein waxy material is polyethylene glycol.

3. The method according to claim 2 wherein polyethylene glycol (PEG) is selected from PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like.

4. The method according to claim 3 wherein polyethylene glycol is PEG 6000.

5. The method according to claim 1 wherein coating of solid waxy material is applied using hot melt technique.

6. The method according to claim 1 wherein coating of waxy material is applied as a solution/suspension.

7. The method according to claim 6 wherein solution/suspension is prepared in a solvent.

8. The method according to claim 7 wherein solvents are selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

9. The method according to claim 1 wherein the multiple unit system has an inert core.

10. The method according to claim 1 wherein the multiple unit system has a drug containing core.

11. The method according to claim 9 wherein the inert core is a commercially available product selected from sugar sphere, non pareil seed, celpheres and the like.

12. The method according to claim 11 wherein inert core is celphere.

13. The method according to claim 11 wherein inert core is non pareil seed.

14. The method according to claim 9 or 10 wherein core is prepared by the method of extrusion-spheronization.

15. The method according to claim 9 or 10 wherein core is prepared by the method of granulation.

16. The method according to claim 14 wherein extrusion-spheronization is carried out by granulating inert core material with or without other pharmaceutical excipient(s) with binder solution, passing the wet mass through extruder and spheronizing the extrudates.

17. The method according to claim 15 wherein granulation is carried by wetting the dry mix of inert core material with or without other pharmaceutical excipient(s) with binder solution.

18. The method according to claim 16 or 17 wherein inert core material may be selected from insoluble, soluble or swellable material.

19. The method according to claim 18 wherein inert core is prepared from an insoluble material.

20. The method according to claim 19 wherein insoluble material is sand (silicon dioxide), glass microcrystalline cellulose (celpheres) or plastic (polystyrene).

21. The method according to claim 18 wherein inert co e is prepared from a soluble material.

22. The method according to claim 21 wherein soluble material is a sugar selected from glucose, mannitol, lactose, xylitol, sucrose, dextrose and the like.

23. The method according to claim 18 wherein inert core is prepared from a swellable material.

24. The method according to claim 23 wherein swellable material is hydroxypropyl methylcellulose.

25. The method according to claim 9 wherein modified multiple units are prepared by coating inert cores with drug(s) and rate controlling polymer.

26. The method according to claim 9 wherein modified multiple units are prepared by coating inert cores first with drug layer and then with release rate controlling layer.

27. The method according to claim 25 or 26 wherein there is a seal coat between inert core and drug layer.

28. The method according to claim 25 or 26 wherein there is a seal coat between drug layer and rate controlling polymer layer.

29. The method according to claim 10 wherein modified multiple unit is prepared by coating drug containing core with release rate controlling polymer layer.

30. The method according to claim 29 wherein there is a seal coat between drug containing core and release rate controlling polymer layer.

31. The method according to claim 29 or 30 wherein there is a seal coat over rate controlling polymer layer.

32. The method according to claims 25, 26 or 29 wherein the rate controlling polymers are selected from cellulosic polymers, methacrylic acid polymers, waxes, hydroxypropyl methylcellulose phthalate, cellulose acetate, phthalate, cellulose acetate trimellitate, and mixtures thereof.

33. The method according to claim 32 wherein cellulosic polymers include ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and the like.

34. The method according to claim 1 wherein drug(s) is selected from the group consisting of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

35. The method according to claim 34 wherein drugs of the above classes are enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

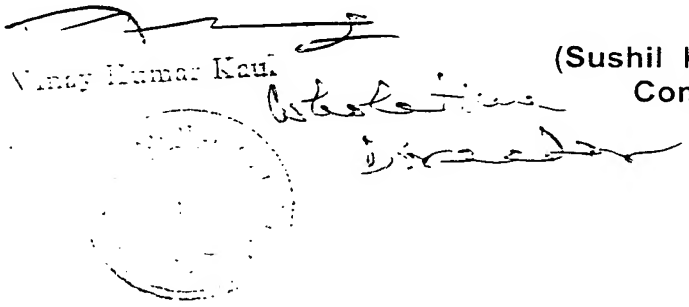
36. The method according to claim 35 wherein drug is venlafaxine.

37. The method according to claim 35 wherein drug is glipizide.

38. A method for preparing modified release multiple unit system comprising a final non-functional coating of polyethylene glycol; which can be easily compressed into tablet or filled into capsule/sachet. without affecting the desired release characteristics of drug as described and illustrated by the examples therein.

Dated this **14TH** day of **November, 2002**.

For Ranbaxy Laboratories Limited



(Sushil Kumar Patawari)
Company Secretary